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Treatment Efficacy of Intermittent Claudication by Surgical Intervention, Supervised Physical Exercise Training Compared to No Treatment in Unselected Randomised Patients I: One Year Results of Functional and Physiological Improvements

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Objectives: *to compare the effect of surgery, exercise and simple observation on maximum exercise power in claudicants.*
Design: *prospective, randomised study.*
Methods: *a total of 264 unselected claudicants were randomised to supervised exercise training, invasive treatment (open surgical or endovascular procedures) or observation. One year treatment outcomes were analysed on an intention to-treat basis.*
Results: *invasively treated patients showed a significant improvement in maximum walking power, stopping distance, post-ischaemic blood flow and big toe pressure at one year. Patients randomised to physical exercise training or to the control group did not improve in any outcome measure.*
Conclusion: *invasive treatment increased walking capacity, leg blood pressure and flow. Supervised physical exercise training offered no therapeutic advantage compared to untreated controls.*

Key Words: Randomised; Intermittent claudication; Exercise; Quality of life; Treadmill.

Introduction

The management of intermittent claudication (IC) is controversial and randomised controlled data is sparse.[1–19] Traditionally, treatment consists of modification of risk factors, and exercise training.[9] Reconstructive surgery is not widely applied, possibly because the restriction to patients' lifestyle has not been considered severe enough to justify the risks.[13] We previously reported that postoperative physical exercise improved walking ability more so than operation alone.[20] The aim of the present study was therefore to evaluate supervised physical exercise training and invasive therapy versus observation (no treatment) in patients with IC at one year follow-up. In a companion paper we also evaluate the impact of the different options on quality of life.

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Methods

Patients presenting intermittent claudication were referred to the vascular surgical outpatient clinic at Sahlgrenska University Hospital, Göteborg, Sweden. All patients were willing to undergo angiography and subsequent operations when offered participation.

Study design

Patients were randomised into one of three groups: control, supervised physical exercise training, or invasive treatment. Patients randomised to the control or training groups were allowed to change group to invasive therapy if requested, provided that their symptoms deteriorated towards severe ischaemia during the course of follow up. All patients were, however, analysed on an intention to-treat basis. Sample size was estimated to include a cohort of patients sufficient in number to allow assessment of treatment outcome of at least 80 patients in each allocated group at one

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year of follow-up based on the experience and power calculations according to the results in our previous interventional studies with three groups, where statistically significant results among 75 randomised patients were obtained.[20]

Inclusion criteria

All patients with stable IC for more than 6 months were evaluated for inclusion. They should have an ankle/brachial index <0.6 and a maximal post-ischaemic calf blood flow <25 ml/min/100 g to be eligible for the study. Patients with a medical history contraindicating surgery and/or with other disorders severely limiting walking evaluation on a treadmill were excluded. A total of 264 unselected patients were included in the study. These patients were randomly recruited from a regional cohort of 400–500 patients between 1994–1997.

Randomisation

Patients were sequentially randomised according to a procedure proposed by Pocock and Simon[21] into three groups, utilising a computer based mathematical algorithm, taking 21 assumed long-term prognostic variables into account. This procedure was deemed necessary since a by chance skewness in assignment could bias interpretations and outcome conclusions. The randomisation was performed by an independent nurse, who communicated the allocation group to the responsible physician. Demographic variables included age, gender, weight, height, smoking habits, presence or absence of diabetes mellitus. Blood chemistry variables were serum creatinine, cholesterol, triglycerides and haemoglobin values. Pressure measurements included systemic arterial blood pressure, systolic ankle pressure and big toe systolic pressure. Physiological testing parameters for stratification were results of exercise ECG, dynamic spirometry, treadmill walking test, and occlusion plethysmography values before and after exercise. Further, presence or absence of groin pulses, duration of symptoms, source of income and dependency of domicilary help were included in the stratification procedure.

Physiological measurements

The walking test was performed on a treadmill with a progressively inclinating slope from 0° to 12° simulating a gradually increasing work load. Treadmill walking capacity was expressed in watts and the maximum walking distance in meters.[22,23] Standard calf blood flow measurements were assessed as maximum post-ischaemic calf blood flow by occlusion plethysmography before treadmill walking.[23] Big toe systolic pressure was measured using a plethysmography technique. Ankle/brachial pressure measurements were determined by standard sphygomanometer where ankle pressure was measured with the aid of a handheld doppler probe.

Blood chemistry

Standard laboratory analyses at Sahlgrenska University Hospital, Göteborg, Sweden were performed to determine levels of haemoglobin, serum creatinine, cholesterol and triglycerides.

Follow-up

After randomisation, the patients were seen at the outpatient clinic and explained the treatment allocation. The first follow-up visit at 6 months after randomisation assessed the clinical status of the patient. The main objective was to monitor any changes in ischaemic symptoms and to evaluate patient and study protocol adherence. The invasive group was also called to a postoperative visit 1 month after interventional therapy. One year after randomisation, the patients' physical status, blood chemistry, pressure and physiological values and health status (see companion paper) were reassessed.

Treatment Groups

All patients were advised to give up smoking and our regular clinical recommendations for risk factor management were followed.[24,25] Planned interventions started within 6 weeks following assignment to the study groups.

Control group

Control patients received no other specific advice or treatment apart from the general advice given to the two treatment groups. Six patients could not adhere to the control group as the presenting claudicating symptoms worsened to such a degree that they demanded invasive therapy.

Table 1. Invasive treatment group: Surgical procedures, patency rates and compliance, $n=76$.

Type of procedure	No of procedure	Patency at 1 year (%)
Total number of interventions	61	82
Aorto/iliaco-femoral by-pass	18	18/18
Endarterectomy (EA) of aorta/iliaca	2	2/2
Iliaca angioplasty	6	3/6
Axillo-femoral by-pass	1	1/1
Procedures above inguinal ligament, total	27	24/27 (89%)
EA $\pm$ patch femoral artery/profundaplasty	2	1/2
Angioplasty superficial femoral artery	11	7/11
Femoro-popliteal synthetic by-pass above knee	11	9/11
Femoro-popliteal vein by-pass above knee	4	3/4
Femoro-popliteal vein by-pass below knee	4	4/4
Distal vein by-pass	2	2/2
Procedures below inguinal ligament, total	34	26/34 (76%)

Table 2. Compliance to treatment allocation of 225 patients attending evaluation 1 year after randomisation.

	Control 76	Training 73	Intervention 76
Requested change to invasive treatment	6*	9*	NA
Unable or unwilling to complete allocated treatment	NA	21	15#
Completed treatment as allocated	70	43	61

* Changed group due to deterioration of symptoms.
\# Did not complete allocated treatment on technical or medical grounds. For further details, see Table 5.
NA: not applicable.

Table 3. Fate of randomised patients during first year of allocated treatment.

	Control 89	Training 88	Intervention 87
Attrition during first year of follow-up	13	15	11
Causes for attrition:			
Death	4	5	5
Amputated	2	0	1
Lost to follow-up	5	7	3
Disabling intercurrent disease prohibiting follow-up*	1	2	2
Misdiagnosis#	1	1	0

* Disabling stroke, severe Parkinson's disease, senility, hip arthrosis.
\# Spinal stenosis.

Supervised physical exercise group

Patients randomised to supervised exercise training classes were referred by the responsible physician (A-G D) to specially designed physical training classes under the supervision of trained physiotherapists. The training program consisted of three 30 min sessions of specific walking training per week during the initial 6 months with 10–12 patients participating in each training class as described.[15] After 6 months two sessions per week were offered.[16] In addition to supervised training, patients were encouraged to undertake individual training programs. During the formal course of their training some patients opted for individualised program that accommodated their specific needs.

Invasive treatment group

Patients randomised to invasive therapy were referred for standard angiography. Based on the angiographic findings, the appropriate intervention, either an endovascular or open surgical procedure was determined according to current surgical management policy. A variety of surgical procedures were performed, and a total of 15 randomised patients (17%) were considered unsuitable for invasive therapy (Table 1). Patients with stenoses and/or short occlusions ≤ 3 cm of the iliac arteries and femoral artery stenoses and occlusion ≤ 5 cm were usually deemed suitable for endovascular treatment. The choice of open surgical operations was made in accordance with our clinical practice. All vein grafts were utilised with the *in-situ* technique and if judged necessary, the grafts were taken below the knee to provide for an optimal run-off. Altogether there were four reconstructions below the knee and two patients received crural by-passes, although by-pass to less than optimal crural arteries was rejected in two cases.

Four cases of planned intervention were abandoned intraoperatively due to: popliteal artery inadequate (2), vein inadequate (1), incongruent operative findings vs angiography (1). Eleven patients were never taken to the operative theatre due to: extensive cardiac risk (3), patient declined operative treatment (3), contrast allergy (2), normal angiography (1), angiographic findings not suitable (2).

Characteristics of the 264 randomised patients are summarised in Table 4. The three groups did not differ on any inclusion parameter at baseline demonstrating the power of the algorithm for stratification. A total of 225 of 264 patients were followed up at 1 year, while two patients experienced 10–12 months follow-up, but are included. Of the 39 patients not completing 1 year follow-up, 14 had died, 15 were lost to follow-up, 3 underwent amputation and 5 were unable to participate in follow-up visits due to disabling intercurrent disease. The number of patients lost to follow-up were similar in the three groups (Tables 2, 3) as

Table 4. Characteristics of 264 unselected patients with intermittent claudication at randomisation. Values are given as mean ± SD when applicable.

	Control 89	Training 88	Intervention 87
Age, years (range)	67 (47–81)	67 (45–81)	66 (38–80)
Gender male/female %	67/33	66/34	64/36
Weight, kg	74.1 ± 13.7	70.1 ± 11.8	73.5 ± 11.3
Height, m	1.70 ± 0.08	1.69 ± 0.08	1.70 ± 0.09
Smoking habits, % yes/ex-smoker/no	49/34/17	53/34/12	52/36/12
Diabetes, %	16	14	19
Systolic blood pressure*	150 ± 24	154 ± 22	155 ± 24
Ankle pressure*	84 ± 19	86 ± 20	85 ± 17
Ankle/brachial index	0.56	0.56	0.55
Systolic big toe pressure*	53 ± 17	55 ± 22	54 ± 19
Maximum exercise power, Watts	94 ± 38	89 ± 35	91 ± 44
Maximum treadmill walking distance, metres	272 ± 153	258 ± 142	274 ± 172
Maximum post-ischaemic calf blood flow, ml/min/100 g	13.3 ± 6.1	13.1 ± 8.5	13.5 ± 7.9
Haemoglobin (132–166)** $g\,l^{-1}$	146 ± 11	147 ± 12	144 ± 13
Cholesterol (2.3–8.5)** $\mu mol\,l^{-1}$	7.0 ± 1.9	6.9 ± 1.5	6.6 ± 1.4
Triglycerides (0.5–1.6)** $\mu mol\,l^{-1}$	2.1 ± 1.0	2.2 ± 1.2	2.1 ± 1.0
Creatinine (60–120)** $\mu mol\,l^{-1}$	103 ± 24	99 ± 23	103 ± 26

* mmHg.
** Values within parentheses normal reference values.

the causes of attrition during the first year of follow-up.

Ethics
Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of the Medical Faculty, Göteborg University, Sweden.

Statistical methods
Patients were only analysed on an intention-to-treat basis (Tables 2, 3). This means that the six patients randomised to the control group and nine patients in the training group, who were subsequently operated upon remained in their original groups during follow-up analyses. Standard descriptive parametric statistics are mean ± SD. Between-group comparisons were performed at 1 year follow-up by the non-parametric Kruskal–Wallis analysis of variance. p values of less than 0.05 are indicated as statistically significant, but $p<0.01$ was deemed necessary for a statistically significant out-fall due to the large number of minimisation factor in the randomisation assignment and to reduce the risk for multiple comparison significance. Maximum exercise power in watts was the primary end point variable in this study.

Results

Mortality compliance, amputation and patency

The mortality rate did not differ among study and control patients, and the mortality rate (5.6%) and the amputation rate (2.2%) in the control group was similar to the natural course for patients with intermittent claudication known from epidemiological data in the literature.[12]

Of 73 patients examinable at 1 year, nine patients in the exercise group underwent interventional therapy due to worsening of symptoms. These patients had significantly lower values than the other patients in the cohort allocated to this group on treadmill performance testing and maximum walking distance (73 vs 89 Watt and 193 vs 258 m respectively), post-ischaemic flow measurements (7 vs 13 ml/min/100 g) and toe pressure measurements (42 vs 55 mmHg). Of the remaining 64 patients, 21 were unwilling or unable to complete the prescribed training program for a number of reasons. The most frequent cause was that after attending a few classes patients were unable to keep up with proposed training schedule. Hence, 43 of 73 (59%) patients finalised their exercise program as prescribed.

At 1 year follow-up, 89% of supra-inguinal reconstructions were patent (24 out of 27), whereas only 76% (26 of 34) of infra-inguinal reconstructions were judged patent on clinical assessment with pulse palpation and handheld doppler examination. Femoral pulse quality on palpation in patients with completed 1 year follow-up was normal in 47% of controls, 52% of exercised patients and in 41% of surgical patients, and was reduced/absent in 53%, 48% and 59% respectively. Failures in patency were mainly found in the superficial femoral artery segment treated either by endovascular intervention or by synthetic grafts placed in the above knee position. All vein grafts placed above or below knee and all distal by-passes were patent except one case.

Physiological results (Table 5, Figs 1–3)

At 1 year follow-up, significant improvement was found for physiological parameters in the invasively treated group only. Hence, treadmill exercise power (Fig. 1) maximum treadmill walking distance, maximum post-ischaemic calf blood flow following treadmill exercise (Fig. 2) and big toe systolic pressure (Fig. 3) improved, as did ankle-brachial index (ABI-Table 5). No improvement in these parameters occurred in the training or control group.

Table 5. Characteristics and results on intention-to-treat basis of 225 randomised patients at 1 year follow-up. Results are given as mean ± SD when applicable.

	Control 76	Training 73	Intervention 76
Systolic blood pressure mmHg	154 ± 29	158 ± 28	161 ± 35
Ankle/brachial index	0.53	0.54	0.71*
Maximum treadmill walking distance, metres	261 ± 131	247 ± 111	344 ± 169*
Haemoglobin (132–166)† $g\,l^{-1}$	144 ± 12	140 ± 21	140 ± 14
Cholesterol (2.3–8.5)† $\mu mol\,l^{-1}$	6.4 ± 1.6	6.6 ± 1.4	6.5 ± 1.2
Triglycerides (0.5–1.6)† $\mu mol\,l^{-1}$	2.0 ± 1.1	1.9 ± 1.2	2.1 ± 1.4
Creatinine (60–120)† $\mu mol\,l^{-1}$	102 ± 32	102 ± 25	107 ± 36

* Denotes statistically significant difference. $p<0.01$.
† Values within parentheses normal reference values.

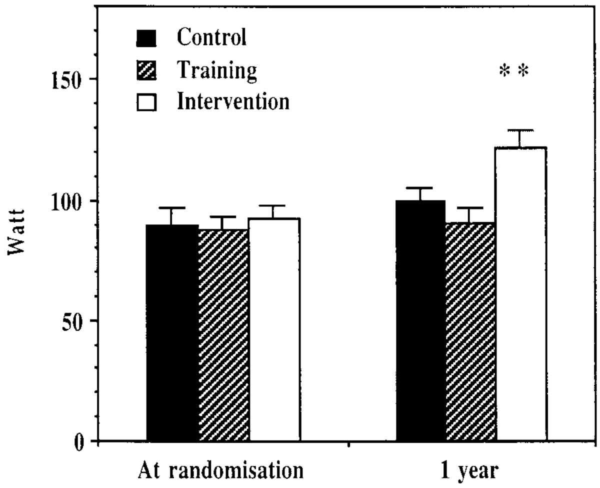

Fig. 1. Maximum exercise power (watt) in treadmill walking before randomisation and at 1 year follow-up. A significant between group difference was noted at 1 year follow-up. ** $p<0.002$.

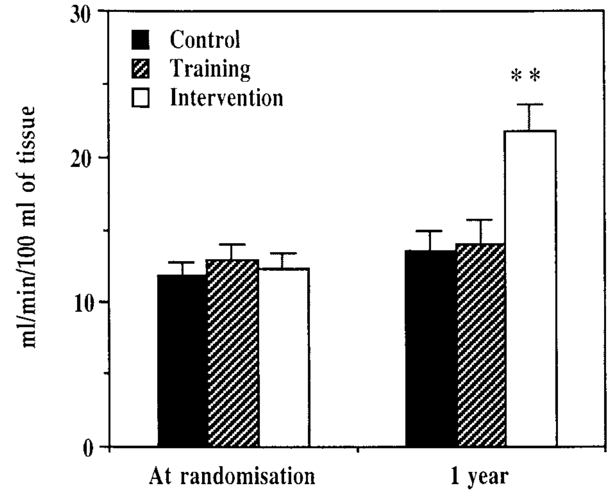

Fig. 2. Maximum post-ischaemic calf blood flow before randomisation and at 1 year of follow-up. A significant between group difference was noted at 1 year follow-up. ** $p<0.001$.

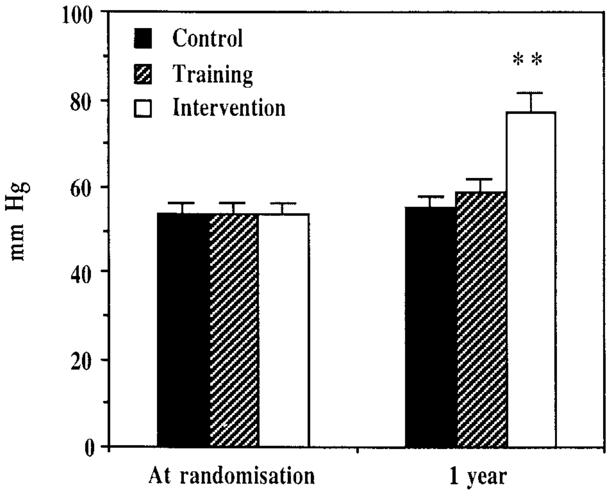

Fig. 3. Systolic big toe pressure before randomisation and at 1 year of follow-up. A significant between group difference was observed at 1 year follow-up. ** $p<0.001$.

Discussion

Claudication is considered a life-style limiting condition rather than a threat to life or limb. The limitation in walking ability, assessed by treadmill, shows IC patients to be disadvantaged to a similar degree as patients with angina pectoris recommended coronary arterial by-pass surgery.[25] Thus, treatment strategies in claudication aim primarily at symptomatic relief. Treatment options, apart from reduction of risk factors, are invasive therapy, exercise training and pharmacological treatment.[9,16,24] However, there is no reported treatment for IC with scientifically proven efficacy in unselected groups of claudication patients.[26] Patients enrolled in the present trial were therefore consecutively referred to the vascular clinic for IC as their dominant presenting symptom. Our results do not support an old notion that a failed surgical procedure might compromise the claudicants' prospect of a later viable limb. Loss of life or limb in the entire cohort of patients was similar among the three treatment groups without difference to the natural course of the disease known from epidemiological surveys.[12] The comparatively large number of "cross overs" following the initial assignments do not limit our conclusions, since surgical intervention (the final treatment option) appeared to be the most effective therapy. Thus, falsely improved outcome in the observational and physical exercise group did not appear following evaluation by intention to treat.

A number of studies on exercise therapy report significant improvements in walking distances.[9,15,16] However, the reasons for improvements have usually remained unexplained as most studies fail to demonstrate any improvement in blood flow or ankle pressure, although widening of the femoral A-V oxygen content may occur. Factors like improved general well-being, blood rheology and muscular enzymatic oxidative capacity have been suggested for improved pain-free walking distance.[18] Although studies on supervised physical exercise training support its benefit, the evidence is based on either uncontrolled or small randomised studies in selected groups of patients.[20] A recent meta-analysis[9] on exercise programs concluded that the greatest improvement in walking distance was achieved with supervised programs lasting 30 min three times a week for at least 6 months. Information was not supplied regarding how long the effects of exercise benefited the patients, treatment costs or compliance to physical training. Furthermore, no attempt was made to translate a statistically significant improvement in metres to clinically meaningful implications,[27] which was included in our present protocol with quality of life evaluations.

Several studies have addressed the issue of increasing use of angioplasty for the treatment of claudication.[7,28–32] The threshold to recommend interventional therapy is largely dependent on availability and resources. All previous publications on treatment outcome of IC applying endovascular/operative procedures or physical training have again focused on selected patients, suitable for the proposed treatment. Our present study differs since an unselected cohort of patients was randomised to one of three options before any pre-treatment investigation had been carried out. In this way we were able to allocate patients in an unbiased fashion and to evaluate the results of treatment on an intention-to-treat basis. Compliance to the allocated treatment was also analysed. Only 43 of the initial 88 patients (49%) randomised to physical training were able to complete the prescribed 6 months of physical training, which may explain the unexpected overall outcome of our study.[33] This finding suggested that efficacious physical training in elderly patients with IC is difficult to fulfil. By the same token, only 59% of the patients allocated to invasive treatment were able to complete the treatment, which underscores the complexity of treating patients with vascular disease in an unbiased study fashion.[34] It is important to emphasise that our study was not designed to compare the results and efficiency of different invasive procedures. The approach was to recommend the most appropriate invasive procedure to relieve the claudicating symptoms by improving limb circulation. Based on the angiography, patients were either referred to the radiology department for endovascular treatment if the lesions were found to be suitable for angioplasty, or to open surgery.

In conclusion, only invasive therapy (surgery or angioplasty) improved circulation in unselected patients with intermittent claudication to an extent, which led to functional improvement in walking ability and maximum exercise power. Improvement in circulatory parameters like big toe pressure and post-exercise maximum calf blood flow values supported the functionally based improvements. Conservative applications (supervised training, observation) had no such impact. The results in the exercise group did not differ from the results in the observational control group. One explanation for this unexpected outcome may be that compliance to training programs is too low in unselected groups of patients with vascular disease. Another explanation may be that regular exercise is actually ineffective in a majority of patients with progressive intermittent claudication. A hesitance to a comparatively short observation time for our patients is limited, since there is no reason to believe that effects of training should appear beyond 1 year only, although the overall effect of surgical intervention may vanish after 1 year. If so, both physical training and surgery would be of little use in treatment of intermittent claudication. Thus, conservative physical training may be regarded inefficient for a majority of patients with intermittent claudication, although it may be beneficial in selected individuals, probably with stable disease.

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